

Locus Coeruleus is associated with higher openness to experience and IQ: implications for the noradrenergic system for novelty seeking in daily life

Emanuele Plini (✉ plinie@tcd.ie)

Trinity College Institute of Neuroscience

Ian Robertson

Meadhbh Brosnan

Paul Dockree

Article

Keywords:

Posted Date: August 16th, 2023

DOI: <https://doi.org/10.21203/rs.3.rs-3222035/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Novelty exposure and the upregulation of the noradrenergic (NA) system have been suggested as crucial for developing cognitive reserve and resilience against neurodegeneration. Openness to Experience (OE), a personality trait associated with interest in novel experiences, may play a key role in facilitating this process. High-OE individuals tend to be more curious and encounter a wider range of novel stimuli throughout lifespan.

To investigate the relationship between OE and the main core of the noradrenergic system, the Locus Coeruleus (LC), as well as its potential mediation of IQ—a measure of cognitive reserve—MRI structural analyses were conducted on 135 healthy young adults. Compared to other neuromodulators' seeds, such as Dorsal and Median Raphe (DR-MR) -5-HT, Ventral Tegmental Area (VTA) -DA-, and Nucleus Basalis of Meynert (NBM) -Ach-, the results indicated that higher LC signal intensity correlated with greater OE and IQ. Furthermore, mediation analyses revealed that only LC played a mediating role between OE and IQ.

These findings shed light on the neurobiology of personality and emphasize the importance of LC-NA system integrity in novelty-seeking behavior. They provide a psychobiological explanation for how OE expression can contribute to the maintenance of the noradrenergic system, enhancing cognitive reserve and resilience against neurodegeneration.

Introduction

A person's ability to flexibly deploy their cognitive resources to offset the effects of natural age-related decline or neurodegenerative disease is described as cognitive reserve (CR) (Stern 2009; Cabeza et al. 2018; Stern et al. 2020). There are important inter-individual differences in cognitive ability emerging in younger adults that are shaped by lifetime experiences, some of which may offer protection from neuropathology later in life (Livingston et al. 2020). The main proxies of CR are socio-behavioural variables including educational status, occupational attainment, intelligence quotient (IQ), and cognitive efficiency measured using standardized neuropsychological tests (Stern et al. 2020). However, several findings (Cutler and Graf 2007; Franchow et al. 2013; Ihle et al. 2019; Karsazi et al. 2021) suggest that a particular personality trait – openness to experience (OE) – may also enhance resilience to cognitive impairment in older adults. A possible explanation is that because high openness promotes a receptivity to novel experiences, which are pursued with high interest, this necessitates flexible cognitive engagement with the world. Conversely, a person who scores lower on the openness trait is more inflexible in their daily routine and more fixed in their beliefs and attitudes.

Scoring higher on the OE trait is also associated with greater IQ levels (fluid and crystallized/verbal) in both younger and older adults (Rammstedt et al. 2018; Schretlen et al. 2010; Ackerman and Heggestad 1997) and is inversely related to Alzheimer's disease (AD) biomarkers (Tautvydaite et al. 2017), suggesting that this personal disposition might be related to better cognitive and biological health outcomes. Similarly, a study of 845 older adults found that, over a period of twenty years, OE was found to be protective against cognitive slowdown (Sharp et al. 2010). Openness is also not entirely fixed in its expression over time, and it has been demonstrated that thirty weeks of a cognitive training intervention can increase scores on the OE scale (Jackson et al. 2012). Taken together, these findings suggest that openness is an important dispositional factor that is related to key cognitive reserve proxies and has a role in shaping the resilience trajectory in the course of healthy and pathological ageing.

The extent to which the personal disposition of openness and the construct of reserve are related through a common neurobiological mechanism is not currently known. However, Robertson (Robertson 2013&2014) has

postulated that the continuous activation (and the related integrity) of the Locus Coeruleus – noradrenergic system (the main source of noradrenaline -NA- in the brain) could be a key candidate affecting cognitive reserve and resilience capabilities. Specifically, it is hypothesized that the continuous upregulation of the noradrenergic system through cognitive stimulation and exposure to novelty might be one of the key neurobiological components for building cognitive reserve, and therefore resilience to neurodegenerative pathologies across the lifespan. In the last decades several studies reported that the LC-NA system integrity was related to greater brain and cognitive health (Wilson et al. 2013; Elman et al. 2021; Jacobs et al. 2021; Plini et al. 2021; Dahl et al. 2022), particularly to better attentive and mnemonic functions both in healthy and clinical populations (Clewett et al. 2016; Dahl et al. 2019; Dutt et al. 2021; Plini et al. 2021).

There are two potential reasons why OE may be associated with repeated activation of the LC-NA system. Firstly, openness promotes exploration of our environment in pursuit of novelty (<https://dictionary.apa.org/openness-to-experience>). The LC appears to underlie novelty signaling patterns, which project to new network configurations within the hippocampus when encoding new vs. familiar experiential episodes (Grella et al 2019). It has also been demonstrated in animal studies that exposure to repeated novel stimuli is a key factor underpinning the benefits of environmental enrichment upon memory function (Sara et al. 1994; Naka et al. 2002; Grilli et al. 2009). Blocking noradrenergic transmission pharmacologically disrupts the benefits of this novelty recognition (Sara et al. 1994; Veyrac et al 2009). In the longer term, repeated phasic NA responding causes greater LC innervation and metabolic health, increasing autophagic factors, which are linked to reduced AD pathology (Omoluabi et al. 2021). Secondly, a receptive and open mind depends on cognitive flexibility (Robertson 2013&2014; Chen et al. 2019). The LC-NA system is hypothesized to underlie an antagonistic relationship between exploitative vs. explorative states. The adaptive gain theory (Aston-Jones & Cohen, 2005) proposes that phasic LC activity is driven by an exploit mode for prioritising goal- or task-related information. When the utility of the current goal wanes, a tonic pattern of LC activity emerges that is associated with an exploratory mode promoting search for other alternative behaviours. Flexibly shifting between explore and exploit modes is a neurobehavioural mechanism that could plausibly support the trait of openness, which also varies along an exploration-exploitation dimension (these cognitive operations are typically also involved in problem solving capability and IQ expression – Birney and Beckmann 2022; Colom et al. 2010; Robertson 2013 & 2014). Narrowing of openness is associated with exploiting familiar routines and behaviours whereas an expansion of openness is an exploratory mode promoting curiosity-led behaviours (Herz et al 2020).

The aim of the current study is to test the noradrenergic theory of cognitive reserve by investigating whether the signal intensity (a parameter of tissue density – integrity) of the LC in humans (measured by voxel-based morphometry - Ashburner and Friston 2000) is related to the expression of the OE trait measured by using the NEO - Five Factor Personality Inventory - NEO-FFI (Costa & McCrae 1992). Specifically, it is hypothesized that people with higher expression of the OE trait will have greater LC signal intensity (as a proxy of tissue density - integrity) because they are more likely to engage with a set of noradrenergically-mediated behaviours that promote mechanisms such as neurogenesis and synaptogenesis within the LC-NA system (Robertson 2013&2014; Mather 2021). Personality, as a relatively stable construct across the lifetime that shapes behaviour on a daily basis (Sutin et al. 2011; Fleeson and Gallagher 2009; Martin et al. 2007; Rhodes et al. 2006), is well positioned to build reserve and neuroprotective effects against disease from a young age. Indeed, it is known that AD pathology is found in healthy brains even from the second and third decades of life (Braak et al. 2011). A secondary aim of this study was to investigate whether LC signal intensity IQ are related, and whether the mediation of the LC-NA system may help explain the relationship between the OE trait and IQ, which is already reported in literature (Moutafi et al. 2006;

Anglim et al. 2022; De Young et al 2020; Bartles et al. 2012; Rammstedt et al. 2018; Schretlen et al. 2010; Ackerman and Heggestad 1997).

The current study will apply Voxel Based Morphometry (VBM) analyses utilizing 3Tesla T1-weighted MRI scans from 135 healthy young subjects (age range 20–35; 96 males, 39 females) derived from the LEMON (*Leipzig Study for Mind-Body-Emotion Interactions*) dataset (Bayaban et al. 2019). The relationship between the structural signal intensity of the LC and the OE trait was examined, and as a control procedure, the relationships between the LC and the other four dimensions of the Big Five personality inventory were also tested. Finally, to assess the differential contribution of neuromodulators to the OE trait, the specificity of the noradrenergic hypothesis was tested using VBM to measure the relative involvement of the other main neuromodulatory subcortical nuclei projecting to the cortex (Dorsal Raphe [DR] and Median Raphe [MR] 5-HT; Ventral Tegmental Area [VTA] DA; and Nucleus Basalis of Meynert [NBM] Ach) to the expression of the OE trait. The same models were repeated while investigating the relationship between LC and IQ.

Methods

The data were provided by Max Plank Institute (<https://www.mpg.de/en>) from the LEMON dataset by Babayan et al. (2019). The behavioural data were downloaded from nitrc.org (https://fcon_1000.projects.nitrc.org/indi/retro/MPI_LEMON.html accessed in July 2020), and the raw MRI data were downloaded from the following source between July and September 2020 https://fcon_1000.projects.nitrc.org/indi/retro/MPI_LEMON/downloads/download_MRI.html. The behavioural data including neuropsychological, psychological and medical variables were manually merged as to build a comprehensive sheet for all the subjects comprised in the LEMON initiative. The analyses were carried out only on the subjects between 20 to 35 years old age range (n.39 females, n.96 males). Subjects with current psychological and psychiatric disorders, such as anorexia, depression and substance abuse, were excluded.

Personality Measure and IQ:

Personality traits were assessed using the NEO-FFI questionnaire by Costa & McCrae 1992 (Costa & McCrae 1992). The NEO-FFI is a 44 items self-report measures on Likert scale (1 to 5) investigating the five main components of personality: Openness to Experience (OE), Conscientiousness (C), Extraversion (E), Agreeableness (A) and Neuroticism (N). Each trait mirrors different personological attitudes, and the interaction between these five dimensions defines personality profiles. Greater values reported reflect greater adherence to the items of the five facets. For example, people who scores high in C, are more likely to be well organized and not impulsive, while people that scores high in E are more prone to be assertive and highly sociable. On the other hand, individuals with high scores in N tend to be irritable, shy and moody while low scores A indicate antagonism, lack of compassion and stubbornness. As described earlier, high scores in OE are informative about the disposition to be open minded, prone to creativity and willing to engage new experiences. Conversely, people who score low in OE are generally disposed to routine, to conservative thinking and tend to avoid changes and challenges.

Intelligence Quotient (IQ) was measured using the WST - Wortschatztest – vocabulary test (Schmid et al. 1992), which is a multiple-choice vocabulary test capable to estimate verbal “crystallized” intelligence on the base of

vocabulary knowledge. The test consists of discriminating non-existing words among real words. In **table 1** the average personality trait scale levels and IQ values together with TIV are reported.

MRI data processing:

3Tesla high-res T1-weighted images in Nifti format underwent a preliminary manual quality control to detect major motion or reconstruction artefacts. This procedure was carried out referring to the rating scale guidelines (1= poor, 2= fair, 3= good, 4= excellent) of the Human Connectome Project (HCP) (<https://www.humanconnectome.org/>). Subjects with low definition (excessive blurriness) and/or marked ringing, inhomogeneities and motion artefacts were removed from the dataset. In order to perform volumetric analyses, the images were processed using CAT12 (Computational Anatomy Toolbox - <http://www.neuro.uni-jena.de/cat/>) implemented in SPM12. The segmentation was run following the default CAT12 settings, except for the voxel size that was settled at 1mm isotropic voxel size. On completion of this process, 135 young subjects (96 males, 39 females) out of 153 were considered suitable for the analyses. The processed and modulated whole brain images (MNI grey matter + white matter) were smoothed using SPM12 interface with a 2 mm³ FWHM kernel. Lastly, to better account for individual volumetric variability in the Voxel Based Morphometry (VBM) analyses, the Total Intracranial Volume (TIV) was calculated for each subject using CAT12 interface (Statistical Analyses – Estimate TIV).

Neuromodulator's region of interest (ROI) masks:

As described in detail in our previous work (Plini et al. 2021), the ROIs were developed on the base of previously published atlases. The ROIs were symmetrically corrected from the original atlases in order to avoid overlapping borders with other structures and to avoid possible biases of “induced lateralization”. All the ROIs were 1mm³ isotropic voxel size and oriented in the Montreal Neurological Institute – MNI – space as the processed images of CAT12. See **figure 1** for ROI's volumetric info. For the current study it was used the LC “omni-comprehensive” probabilistic mask we developed earlier (Plini et al. 2021). The “omni-comprehensive” LC mask solves the inconsistent LC spatial localization reported by previous works (Keren et al. 2009 & 2015; Tona et al. 2017; Betts et al. 2017; Dahl et al. 2019; Liu et al. 2019; Rong Ye et al. 2020; Dahl et al. 2021), while enabling to comprise the whole anatomical LC regions defined across lifespan, without encroaching other pontine and cerebellar regions, and without crossing the walls of the 4th ventricles (further details can be found in supplementary materials of Plini et al. 2021 and at this link: <https://www.youtube.com/watch?v=90bsA6Jqxs4>). The MR and DR ROIs were provided by Beliveau et al. (Beliveau et al. 2015), the VTA mask was obtained by downloading the VTA MNI probabilistic map from the atlas made by Pauli et al. 2018 (Pauli et al. 2018) from the NeuroVault website (<https://neurovault.org/> accessed on 15 December 2018). The NMB was developed on the base of the probabilistic MNI maps of the acetylcholine cells of the Forebrain are provided by SPM Anatomy Toolbox 2.2c (https://www.fzjuelich.de/inm/inm1/EN/Forschung/_docs/SPMANatomyToolbox/SPMANatomyToolbox_node.html accessed on 15 December 2018) by Zaborszky et al. 2008 and George et al. 2011, Schulz et al. 2018, Liu et al. 2015, Kilimann et al. 2014, Koulousakis et al. 2019.

VBM analyses:

Using the processed and smoothed whole brain images, the VBM analyses were carried out in CAT12 (basic models) implementing multiple regression models. The analyses were divided into two main branches. The first one investigated the LC-NA system and the five personality traits of NEO-FFI in five different statistical models

(Openness to Experience, Conscientiousness, Extraversion, Agreeableness, Neuroticism). The second one investigated the relationship between the LC-NA system and I.Q (WST - Wortschatztest – vocabulary). All the analyses followed the same procedures and had the same set of continuous covariates (age, TIV, gender). After the estimation of the statistical models (“estimating the statistical model”) and after checking for the design orthogonality (“checking for design orthogonality”), the “results” were checked using the following contrast in the SPM12 “contrast interface”: 0 0 0 0 1 (for positive relationship) and 0 0 0 0 -1 (for negative relationship). Both relationships were always tested as to control the reliability of the findings. A further step in the analyses pipeline was to indicate the LC binary mask as inclusive mask to isolate the LC involvement in the models. Eventually the statistical threshold was settled at $P < 0.01$, and later increased progressively until the results disappeared (namely: $P < 0.001$, $P < 0.05$ family wise error corrected – FWE). Each set of analyses, after having examined the LC, was systematically repeated considering the other ROIs’ binary masks in this order: DR, MR, VTA and NBM as controlling assurance for the LC findings.

In order to perform Bayesian analyses, the average signal intensity of the ROIs was extracted in FSL by using the binary masks on the smoothed (2 mm^3 FWHM kernel) whole brain images. In FSL terminal, the flags of “fslstats” “-k” (mask) and “-m” (output mean) were used to gather the average voxel intensities for each ROI subject by subject. This procedure was also carried out to extract the average signal intensity from clusters of significant voxels outcoming from the VBM analyses in order to calculate more accurate Bayes Factors (BF) and to perform mediation analyses.

Bayesian modelling and correlation matrices and partial correlations

In JASP (<https://jasp-stats.org/>), a Bayesian model was performed to compare within the same model the differential strengths of the neuromodulators predicting OE (linear regression model, OE entered as dependent variable, and the five ROIs as covariates). TIV, age and gender were also included and added to the ‘null model’. The differential relationship of the five ROIs were compared with the null model, and the analyses were run with default parameters with the only exception of Bayesian information criteria (BIC) selected in the advanced option of JASP interface. The same models were run for the other personality traits.

Both Bayesian and Pearson’s correlation matrices were built considering the following continuous variables: Openness to Experience, Conscientiousness, Extraversion, Agreeableness, Neuroticism, WST-IQ, and the five personality traits with the STAI-G-X2 anxiety scale and Perceived Stress Questionnaire (PSQ). Similarly STAI-G-X2 and PSQ were entered in a correlation matrix with LC, MR, DR, MR, VTA, NBM to explore possible relationship with the neuromodulatory subcortical system. BF were generated in the JASP interface (Bayesian correlation model) on the base of the average signal intensity of the significant clusters outcoming from the VBM analyses (when the ROIs were surviving the statistical thresholds settled). The average signal intensity of the whole ROI was considered in the Bayesian correlation matrices only for the ROIs, which showed no significant cluster of voxels in the VBM analyses. Finally, partial correlations were performed in SPSS 25 (<https://www.ibm.com/products/spss-statistics>). The relationships between LC and IQ was controlled for OE in two different batches, first from the LC-IQ relationship OE was regressed out, then from the LC-OE relationship the effect of IQ was regressed out. These analyses had the aim to better differentiate the LC variance across these different domains.

Lastly, to better investigate the association between OE and LC signal intensity, in an ANCOVA model, OE trait was treated as independent factor divided in 3 levels (low, mid and high OE expression) and the LC was treated as

dependent continuous variable while controlling for age, gender and TIV. Post-hoc analyses both applied Tuckey and Bonferroni corrections.

Mediation analyses

Mediation analyses with parallel multiple mediators (model 4) was carried out in SPSS using the PROCESS toolbox by Andrew Hayes. OE was entered as predictor (Y) and IQ (X) as outcome in accordance with our framework conceiving that greater OE may induce greater IQ levels because novelty exposure and cognitive stimulation via the noradrenergic system. This model is also consistent with certain evidence considering IQ as a subcomponent of OE and while being related to OE across various studies (Moutafi et al. 2006; Anglim et al. 2022; De Young et al 2020; Bartles et al. 2012).

As multiple mediators, the average signal intensity of LC, MR, DR, VTA and NBM were entered. The models were covaried for age, TIV and gender. Standard model was set with 95% confidence intervals and 10000 bootstrap samples.

Results

1st branch of VBM analyses: relationship between neuromodulators' signal intensity and BIG-5 personality traits

- Does the LC signal intensity predict Openness to Experience values relative to other neuromodulator seed regions?

As can be observed in **table 2**, across the 135 healthy subjects, LC signal intensity was the strongest predictor of the OE personality trait compared to the other neuromodulators, while controlling for age, gender and TIV. Two large bilateral clusters, for a total of 153 voxels within the LC region, positively related to greater OE values for $p < 0.01$ threshold. As shown in **figure 2**, the spatial localizations of the LC results overlapped the LC region defined by the previously published LC atlases and masks (Keren et al. 2009 & 2015; Tona et al. 2017; Betts et al. 2017; Dahl et al. 2019; Liu et al. 2019; Rong Ye et al. 2020; Dahl et al. 2021; Garcia-Gomar et al. 2022). By increasing the statistical threshold up to $p < 0.001$ only a cluster of 22 voxels survived in the LC core. However, no LC voxels remained when FWE correction was applied.

Regarding other personality traits, 67 voxels within the LC region were associated with Conscientiousness. Only 5 voxels of the LC clusters survived when more conservative thresholds were set ($p < 0.001$), however the cluster did not survive FWE correction. In table n.2, the minor and negligible associations between the five ROIs and the other personality traits are reported in detail.

As control procedure, when the opposite relationships were tested, no associations were found between the LC and five personality traits, neither for the other ROIs. The only exception (not reported in tables) was the negative relationship between the VTA and Conscientiousness. Lower VTA signal intensity (68 voxels) related to greater Conscientiousness values. However, this result did not survive the $p < 0.001$ threshold.

Treating Openness to experience as a factor

As can be observed in **table 2b**, different levels of OE expression are associated with greater LC signal intensity. Low OE expression (scores below 2) are associated with lesser LC signal intensity while high OE expression (scores above 3) are associated with greater LC signal intensity ($P < 0.05$ Bonferroni corrected). This model reports a moderate effect size (Cohen's $d = 0.486$).

2nd branch of VBM analyses: relationship between neuromodulators' signal intensity and IQ - Does the LC predict IQ relative to other neuromodulator seed regions?

As reported in **table 2**, 23 LC voxels (for $p < 0.01$) mostly left lateralised rostrally were related to greater IQ. The LC spatial localization overlaps the LC core defined in the previously published LC atlases. When the statistical threshold was increased to $p < 0.001$ the cluster disappeared. No associations between IQ and the other ROIs were found, demonstrating specificity for the relationship between IQ and LC. No significant clusters across the five ROIs were found when the opposite relationships were tested.

Using Bayesian modelling to examine single and combined contributions of different neuromodulators

The abovementioned VBM analysis found that the LC was a key predictor of the OE trait. However, a further Bayesian approach provides a means to compare the strength of evidence for different neuromodulator seeds in predicting OE trait scores. Here, we employed a model in which each neuromodulator seed is examined as a standalone predictor and also in a combined way, which compares the predictive strength when different neuromodulator seeds also examined in combination if they explain more variance. The Bayesian linear regression model showed that as standalone variable the LC signal intensity has the strongest relationship with OE against the null model ($BF_{10} \ 338.401 - BF_M \ 9.544$). The combined effect for LC and VTA signal intensity has the strongest relationship among single and combined models ($BF_{10} \ 993.661 - BF_M \ 33.699$) suggesting a disproportionate catecholaminergic involvement in OE trait accounting for 14% (LC alone) - 18% (LC + VTA) of its variance. Moreover, the combined effect of LC and serotonergic DR was the third strongest model related to OE accounting for 17% of variance. A summary of these analyses is reported in detail in **table 3**.

Exploring the relationships between personality, IQ and the Locus Coeruleus

Correlation matrices revealed that among the **five personality** traits only the OE scale related significantly with **IQ**. Specifically, greater OE values related to greater IQ scores (Pearson's $R \ 0.391$, - $BF_{10} \ 3305.75$ - for $p < 0.001$). For greater detail refer to the correlation table in the supplementary materials.

Partial correlations revealed that the relationship between LC and IQ disappeared when the effect of OE trait was regressed out in the model. On the other hand, the relationship between OE trait and LC remained significant when controlling for IQ. These two partial correlations together are suggestive that the relationship between OE and LC might be more stable than the relationship between LC and IQ. For greater detail refer to the partial correlation table in the supplementary materials.

Exploring the relationships between personality, IQ and the Locus Coeruleus

Correlation matrices revealed that among the **five personality** traits only the OE scale related significantly with **IQ**. Specifically, greater OE values related to greater IQ scores (Pearson's $R \ 0.391$, - $BF_{10} \ 3305.75$ - for $p < 0.001$). For greater detail refer to the correlation table in the supplementary materials.

Partial correlations revealed that the relationship between LC and IQ disappeared when the effect of OE trait was regressed out in the model. On the other hand, the relationship between OE trait and LC remained significant when controlling for IQ. These two partial correlations together are suggestive that the relationship between OE and LC

might be more stable than the relationship between LC and IQ. For greater detail refer to the partial correlation table in the supplementary materials.

Mediation analyses with parallel multiple mediators - *Does the LC mediate the relationship between the OE trait level and IQ over the other neuromodulators?*

Mediation analyses with multiple parallel mediators were carried out in order to clarify possible mediation effects of the neuromodulators. While controlling for age, TIV and gender, bootstrap (10000) confidence intervals were used to examine the role of the five subcortical ROIs in mediating the relationship between the OE trait and IQ. Only LC alone significantly mediates the relationship between OE (Y) and IQ (X) indicating that greater OE was predictive of greater IQ score and that this relationship was mediated by the LC and not by the other neuromodulators, which did not mediate this relationship. Indeed, the total indirect effect of the parallel mediators was not significant. These results suggest that the strong relationship found between OE and IQ is disproportionally influenced by the noradrenergic system over the other neuromodulators, as previously observed in the VBM analyses (see **table 4** for details).

Discussions

The present study investigated the relationship between MRI signal intensity of different neuromodulators' seeds and the Five Factor Personality Inventory score in 135 healthy young participants. As hypothesized, greater structural signal intensity of the Locus Coeruleus (LC) was found to be related to higher scores in the Openness to Experience (OE) trait, and with a greater Intelligence Quotient (IQ) score. When neuromodulator seeds were considered together in a Bayesian model, catecholamines (LC + VTA) were the strongest predictor of OE, followed by the LC as stand-alone predictor of OE, and thirdly the LC combined with the serotonergic DR. These findings are the first evidence linking neuromodulatory MRI signal intensity to personality traits.

Given the OE trait is commonly associated with intelligence (both fluid and crystalized/verbal) and is frequently named as the "intellect" trait in the literature (Moutafi et al. 2006; Anglim et al. 2022; De Young et al 2020; Bartles et al. 2012; Rammstedt et al. 2018; DeYoung et al. 2013; Schretlen et al. 2010; DeYoung et al. 2005; Ackerman and Heggstad 1997), we examined the extent to which LC-NA signal intensity might account for this relationship. A mediation analyses revealed that, in comparison with the other neuromodulatory nuclei, only the LC accounted for the relationship between OE and IQ, supporting the assertion that the LC-NA system may be a key neurobiological substrate mediating the relationship between openness to experience and intellectual expansion. We also established that the relationship between the LC and OE remained when the effect of IQ was regressed out, demonstrating that unique variance in the openness trait is associated with LC-NA system signal intensity. Finally, it was apparent that the LC was not exclusively associated with the OE trait. We also observed a weaker relationship between LC and the Conscientiousness (C) scale.

We interpret the key findings of the current study in the context of the Noradrenergic Theory of Cognitive Reserve (Robertson 2013&2014) proposing that more protracted responses to novelty and chronic exposure to enriched environments in high-OE trait individuals is underpinned by the activation of the LC-NA system. Why might novelty be an important factor for increasing LC signal intensity? One potential underlying mechanism could be increased frequency of LC phasic firing in response to novel events. Ghosh and Omoluabi (Ghosh et al. 2021; Omoluabi et al. 2021) examined single unit recordings from the LC during novelty exposure in rats. After six-weeks of LC stimulation (LC phasic activation for 20 minutes five days per week) rats showed increased response to novel

stimuli, and greater LC health (increased macrophage activation and greater LC fiber density), along with increased cognitive functions and reduced AD biomarkers in comparison with rats which did not undergo the LC phasic activation. Rats not exposed to novelty showed greater LC neurodegeneration with increased AD biomarkers and poorer cognitive outcomes. Omoluabi et al. (2021) concluded that LC-phasic firing in response to novelty was protective against the detrimental effect of AD biomarkers (pre-tangle tau production in the LC), preventing LC fiber loss resulting in greater LC axonal integrity and more preserved cognition.

Consistent with the aforementioned animal study, a recent fMRI study in humans carried on 128 healthy individuals from the Harvard aging study (Prokopiou et al. 2022) found LC activity significantly increased while novel stimuli were presented. They also reported that lower novelty-related LC activity was associated with greater cognitive decline related to AD biomarkers levels (beta-amyloid PET). Krebs et al. 2018 have also demonstrated that phasic LC activity when a contextually-unexpected stimulus occurs, namely, a novel stimulus that is incongruent to context.

Although the VBM analyses revealed that the LC was the key predictor of OE, a Bayesian multiple regression model explored the combined effects of LC with the other subcortical nuclei. This analysis revealed that LC + VTA was a stronger predictor of OE than the LC alone. An additive involvement of the dopaminergic system in shaping personality may explain this relationship: exploratory behaviour that characterizes openness will be further reinforced by the reward value of novel experiences via the mesolimbic dopamine system. Alternatively, the role of DA in supporting the OE trait may have a genetic basis as catalyst for the conversion of DA to NA. (Barnes et al. 2011). Furthermore, the role of the DR nucleus, while only a negligible contributor to the model on its own, also combined with the LC to predict OE trait variation. Serotonergic involvement in OE trait expression may involve increased sensitivity to stress during exploration of novel environments. Previous work has found that cerebral 5-HTT levels are associated with OE (Kalbitzer et al 2008; Ren et al. 2021). However, 30% of DR is composed by catecholaminergic neurons (Farley et al. 1977; Baker et al. 1991; Ordway et al. 1997; Kirby et al. 2003), therefore this association might reflect common dopaminergic and noradrenergic involvement in OE expression. Overall, the synergic involvement of these three main neuromodulatory nuclei may contribute to shaping the nature of openness via different pathways – through VTA-DA mediated reward sensitivity, DR-5-HT potentiation of stress-related responses during exposure to novelty, as well as overarching explore-exploit behavioral patterns promoted by the LC-NA system (Tochigi et al. 2005; Zmorzyński et al. 2021; Ren et al. 2021; Deyoung et al. 2008; Deyoung et al. 2011; Deyoung 2013). We observed positive relationships between the signal intensity of such nuclei and OE, therefore these interpretations are based on the assumption that greater structural signal intensity (tissue density – integrity) of these nuclei would ensure an adequate neuromodulatory functioning building the ground for a more developed OE trait. Conversely, lower signal intensity (reduced tissue density – integrity) of these nuclei would undermine the normal neuromodulator biosynthesis underlying OE trait expression. This interpretation is supported by the literature reporting how variations of neuromodulators' concentrations can bidirectionally affect personality traits expression (Tochigi et al. 2005; Narita et al. 2015; Ward et al. 2017; Fischer et al. 2018; Käckemester et al. 2019; Kanen et al. 2021). By contrast, reduced signal intensity of the neuromodulatory subcortical system can result in poorer bioavailability of such neuromodulators (May and Paxinos 2012).

A unique contribution of the LC-NA system in this study was its mediatory role in accounting for a relationship between OE and IQ. This intercorrelation highlights LC-NA system centrality in higher order cognition. Greater IQ and higher OE scores are both conceived as Reserve proxies that reduce the risk of cognitive decline and dementia (Cuttler and Graf 2007; Franchow et al. 2013; Ihle et al. 2019; Karsazi et al. 2021; Rammstedt et al. 2018; Schretlen et al. 2010; Ackerman and Heggestad 1997; Tautvydaite et al. 2017; Sharp et al. 2010). The integrity of the LC-NA

system, given its role in neurodegeneration, might be a common factor contributing to the expression of these two constructs in terms of brain and cognitive health (DeYoung et al. 2013; Robertson 2013&2014). These findings are therefore suggestive that the LC signal intensity even at young age, can significantly affect cognition and personality expression with the potential to build resilience to neurodegeneration in later life. Although the current study is the first to link LC-NA signal intensity to OE, there is previous evidence that the noradrenergic system is associated with greater cognitive performance and intelligence (Tsukahara and Engle 2021; Zhao et al. 2014; Clewett et al. 2016; Liu et al. 2020; Wilson et al. 2013; Elman et al. 2021; Jacobs et al. 2021; Plini et al. 2021; Dahl et al. 2022; Dahl et al. 2019; Dutt et al. 2021).

Although OE showed the strongest relationship to the LC, a secondary VBM association was also observed between the C trait, conscientiousness, and the LC. The C trait, which reflects perseverance and focus, is associated with increased attention performance and reduced speed of processing (Yoneda et al. 2022; Chapman et al. 2017; Sutin et al. 2019) and improved memory (Lucchetti et al. 2016; Allen et al. 2018; Sutin et al. 2019 b). These cognitive domains also implicate LC-NA system integrity and functioning across several studies (Aston-Jones et al. 2000; Aston-Jones and Cohen 2005; Bari et al. 2022; Grueschow et al. 2022; Dahl et al. 2022; Unsworth et al. 2017; Plini et al. 2021). Moreover, further work has found that greater C scores are associated with both greater resistance to Dementia (Yoneda et al. 2022; Kaup et al. 2019). and lower risk of mild cognitive impairment and Alzheimer's Disease (Wilson et al. 2007; Terracciano et al. 2017; Sutin et al. 2018; Aschenbrenner et al. 2020). It should be noted that the role of additional variables needs further investigation. For example, it is documented that individuals who are high in C are more prone to engage regular physical activity (Sutin et al. 2016), which is also known to be related to better brain and cognitive health and to the LC-NA system. Clearer dissociation of the role these different protective factors is warranted.

The current findings demonstrates that the C trait combined with greater OE expression in healthy individuals is associated with greater signal intensity in the LC. It remains to be seen whether these personality traits, through interaction with LC-NA system over the lifespan, provide greater resilience to neurodegeneration. However, these significant clinical implications warrant longitudinal investigation.

Limitations

The main limitation of the current argumentation lays on the cross-sectional nature of the study. A longitudinal study would provide more accurate casual relationships among these variables and would enable to understand possible trajectories. However, personality traits measured by NEO-FFI tend to be stable throughout lifetime (McCrae et al. 2011; Gnambs et al. 2014). This gives us more confidence in the mediation analyses and in the partial correlations, which may help us understand the actual nature of these relationships.

Another potential limitation is selection bias - people who were recruited via the LEMON study might be, by nature of their voluntary participation, individuals who are "highly open" to engage in new experiences and this might limit the representativeness of the sample to general population. This selection bias may also have been exacerbated by excluding individuals with ongoing psychological or psychiatric symptoms. The current sample reported low levels of anxiety, and had a low level of neuroticism compared to other scales such as OE or C. Therefore, the possible detrimental effect of "high tonic" LC firing commonly observed in response to stress and anxiety could affect or reduce the LC-OE relationship and their possible neuroprotective outcomes (Rorabaugh et al. 2017; Ghosh et al. 2021; Omoluabi et al. 2021). Nonetheless, it is worth mentioning we found no relationships between LC signal intensity and anxiety scales which could affect the present set of findings.

Other minor limitations are the relatively small size of the sample, which can explain why the results did not survive the most conservative multiple comparison corrections on a voxel wise approach, while it remained significant after Bonferroni correction on ROI analysis. Lastly, the constraints of the self-report personality questionnaires with forced choices, along with the IQ measured on the base of vocabulary only. However, within these limitations, we made the attempt to account for the confounding variables, controlling for age, gender and TIV. In the same vein, we also systematically tested with numerous control analyses different relationships, and we also tested the antithetic hypothesis to consider the alternative direction of effects. A total of 60 VBM control analyses contrasted to our main analyses yielding greater confidence in the validity of our key findings.

Clinical implications and future directions

Together, these findings are suggestive that personal attitudes to life, captured by the personality of openness (and Conscientiousness), might be influenced, in part, by activation of the noradrenergic system. These findings may provide explanatory ground concerning the neuropsychological dynamics underlining the association between OE and resilience to neurodegenerative diseases while supporting Robertson's theory (Robertson 2013&2014; Tautvydaite et al. 2017; Sharp et al. 2010; Cuttler and Graf 2007; Franchow et al. 2013; Ihle et al. 2019; Karsazi et al. 2021). Indeed, as outlined by Robertson (Robertson 2013&2014), LC-NA system plays an important role underpinning all the attentional processes, and in particular the exposure to novelty along with managing and developing problem-solving skills. This interacting with greater Conscientiousness may ensure consistent cognitive control eliciting optimal noradrenergic tone (Robertson 2013&2014; Aston-Jones et al. 2000; Aston-Jones and Cohen 2005). In keeping with this, a dispositional 'openness' trait might drive a greater noradrenergic tone throughout lifetime, leading to more frequent phasic activation of LC-NA system yielding to greater LC integrity and greater brain and cognitive health (Robertson 2013&2014; Omulabi et al. 2021; Clewett et al. 2016; Dutt et al. 2021; Mather et al. 2021; Plini et al. 2021; Prokopiou et al. 2022). This 'openness' trait throughout lifespan might interact with other reserve variables, such as I.Q. via the mediation of the LC-NA system. Indeed, several studies reported greater OE is linked to greater crystallized intelligence (Rammstedt et al. 2018; Schretlen et al. 2010; Ackerman and Heggestad 1997). Alternatively, it is possible that LC-NA characteristics could contribute to the 'openness' personality characteristic, or that the relationship is explained by other variables. However, the newly established link between personality traits, LC-NA system, and cognition outlines the intercorrelation between neuropsychological variables and opens to potential psychological interventions targeting the LC-NA system. Cognitive and behavioral approaches (Cognitive Behavioral Therapy – CBT) which focus on OE, in people who score low in OE and C, might be considered among the preventing strategies for neurodegenerative diseases (Forgeard et al. 2019). This might be beneficial improving people's well-being both in enhancing the executive/attentional domain (Forgeard et al. 2019; Jackson et al. 2012) and in building the resilience ground to neurodegenerative diseases. Personality traits (OE especially) might be considered as critical component to focus on for brain health potentially influencing the neuroprotective role of LC-NA system particularly in the face of neurodegeneration. Future studies should replicate these findings and design longitudinal investigations considering biological biomarkers, personological and cognitive variables using high-res MRI to better understand the neuropsychological dynamics which underpin our novel findings.

Declarations

Funding

Authors contributions:

ERGP: conceptualization, study design, statistical analyses, results interpretation and visualization, manuscript writing. **IHR:** conceptualization and supervision. **MB:** statistical analyses design and manuscript editing. **PMD:** supervision, result interpretation and manuscript editing.

All authors approved the final version of the manuscript.

Thanks are extended to **Francesca Fabbicatore** for proofreading the manuscript and for the thoughtful comments provided throughout the course.

Conflict of Interest:

The authors declare no conflict of interest

References

1. Ackerman PL, Heggestad ED. Intelligence, personality, and interests: evidence for overlapping traits. *Psychol Bull.* 1997 Mar;121(2):219-45. doi: 10.1037/0033-2909.121.2.219. PMID: 9100487.
2. Allen MS, Laborde S, Walter EE. Health-related behavior mediates the association between personality and memory performance in older adults. *J Appl Gerontol.* 2019;28:232–52.
3. Aschenbrenner AJ, Petros J, McDade E, Wang G, Balota DA, Benzinger TL, Cruchaga C, Goate A, Xiong C, Perrin R, Fagan AM, Graff-Radford N, Ghetti B, Levin J, Weidinger E, Schofield P, Gräber S, Lee JH, Chhatwal JP, Morris JC, Bateman R, Hassenstab J; Dominantly Inherited Alzheimer Network. Relationships between big-five personality factors and Alzheimer's disease pathology in autosomal dominant Alzheimer's disease. *Alzheimers Dement (Amst).* 2020 Jun 23;12(1):e12038. doi: 10.1002/dad2.12038. PMID: 32587883; PMCID: PMC7311802.
4. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. *Neuroimage.* 2000 Jun;11(6 Pt 1):805-21. doi: 10.1006/nimg.2000.0582. PMID: 10860804.
5. Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci.* 2005;28:403-50. doi: 10.1146/annurev.neuro.28.061604.135709. PMID: 16022602.
6. Aston-Jones G, Rajkowski J, Cohen J. Locus coeruleus and regulation of behavioral flexibility and attention. *Prog Brain Res.* 2000;126:165-82. doi: 10.1016/S0079-6123(00)26013-5. PMID: 11105646.

1. Babayan, A., Erbey, M., Kumral, D., Reinelt, J. D., Reiter, ... Villringer, A. (2019). A mind-brain-body dataset of MRI, EEG, cognition, emotion, and peripheral physiology in young and old adults. *Scientific data*, 6, 180308. <https://doi.org/10.1038/sdata.2018.308>
2. Baker K.G., Halliday G.M., Hornung J.P., Geffen L.B., Cotton R.G. Distribution, morphology and number of monoamine-synthesizing and substance P-containing neurons in the human dorsal raphe nucleus. *Neuroscience*. 1991;42:757–775. doi: 10.1016/0306-4522(91)90043-N.
3. Bari A, Xu S, Pignatelli M, Takeuchi D, Feng J, Li Y, Tonegawa S. Differential attentional control mechanisms by two distinct noradrenergic coeruleo-frontal cortical pathways. *Proc Natl Acad Sci U S A*. 2020 Nov 17;117(46):29080-29089. doi: 10.1073/pnas.2015635117. Epub 2020 Nov 2. PMID: 33139568; PMCID: PMC7682591.
4. Barnes JJ, Dean AJ, Nandam LS, O'Connell RG, Bellgrove MA. The molecular genetics of executive function: role of monoamine system genes. *Biol Psychiatry*. 2011 Jun 15;69(12):e127-43. doi: 10.1016/j.biopsych.2010.12.040. Epub 2011 Mar 11. PMID: 21397212.
5. Bartels, M., van Weegen, F. I., van Beijsterveldt, C. E. M., Carlier, M., Polderman, T. J. C., Hoekstra, R. A., & Boomsma, D. I. (2012). The five factor model of personality and intelligence: A twin study on the relationship between the two constructs. *Personality and Individual Differences*, 53(4), 368–373. <https://doi.org/10.1016/j.paid.2012.02.007>
6. Beliveau V., Svarer C., Frokjaer V., Knudsen G.M., Greve D.N., Fisher P.M. Functional connectivity of the dorsal and median raphe nuclei at rest. *NeuroImage*. 2015;116:187–195. doi: 10.1016/j.neuroimage.2015.04.065
7. Betts M.J., Cardenas-Blanco A., Kanowski M., Jessen F., Düzel E. In vivo MRI assessment of the human locus coeruleus along its rostrocaudal extent in young and older adults. *NeuroImage*. 2017;163:150–159. doi: 10.1016/j.neuroimage.2017.09.042
8. Birney DP, Beckmann JF. Intelligence IS Cognitive Flexibility: Why Multilevel Models of Within-Individual Processes Are Needed to Realise This. *J Intell*. 2022 Aug 1;10(3):49. doi: 10.3390/jintelligence10030049. PMID: 35997405; PMCID: PMC9397005.
9. Braak H., Thal D.R., Ghebremedhin E., Del Tredici K. Stages of the pathologic process in Alzheimer disease: Age categories from 1 to 100 years. *J. Neuropathol. Exp. Neurol*. 2011;70:960–969. doi: 10.1097/NEN.0b013e318232a379
10. Cabeza R., Albert M., Belleville S., Craik F.I.M., Duarte A., Grady C.L., Lindenberger U., Nyberg L., Park D.C., Reuter-Lorenz P.A., et al. Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nat. Rev. Neurosci*. 2018;19:772. doi: 10.1038/s41583-018-0068-2.
11. Chapman BP, Benedict RH, Lin F, Roy S, Federoff HJ, Mapstone M. Personality and performance in specific neurocognitive domains among older persons. *Am J Geriatr Psychiatry*. 2017;25(8):900–8.
12. Chen, Xinjie & He, Jinbo & Fan, Xitao. (2019). Relationships between openness to experience, cognitive flexibility, self-esteem, and creativity among bilingual college students in the U.S.. *International Journal of Bilingual Education and Bilingualism*. 10.1080/13670050.2019.1688247.
13. Clewett D.V., Lee T.-H., Greening S., Ponzio A., Margalit E., Mather M. Neuromelanin marks the spot: Identifying a locus coeruleus biomarker of cognitive reserve in healthy aging. *Neurobiol. Aging*. 2016;37:117–126. doi: 10.1016/j.neurobiolaging.2015.09.019.
14. Colom R, Karama S, Jung RE, Haier RJ. Human intelligence and brain networks. *Dialogues Clin Neurosci*. 2010;12(4):489-501. doi: 10.31887/DCNS.2010.12.4/rcolom. PMID: 21319494; PMCID: PMC3181994.

15. Costa PT, McCrae RR (1985). *The NEO Personality Inventory manual*. Odessa, FL: Psychological Assessment Resources.
16. Costa, P. T. & McCrae, R. R. *Revised NEO Personality Inventory (NEO PI-R) and NEO Five Factor Inventory (NEO-FFI) Professional Manual*. (Psychological Assessment Resources Inc., 1992).
17. Cuttler C, Graf P. Personality predicts prospective memory task performance: an adult lifespan study. *Scand J Psychol*. 2007 Jun;48(3):215-31. doi: 10.1111/j.1467-9450.2007.00570.x. PMID: 17518914.
18. Dahl MJ, Mather M, Werkle-Bergner M, Kennedy BL, Guzman S, Hurth K, Miller CA, Qiao Y, Shi Y, Chui HC, Ringman JM. Locus coeruleus integrity is related to tau burden and memory loss in autosomal-dominant Alzheimer's disease. *Neurobiol Aging*. 2022 Apr;112:39-54. doi: 10.1016/j.neurobiolaging.2021.11.006. Epub 2021 Dec 7. PMID: 35045380; PMCID: PMC8976827.
19. Dahl MJ, Mather M, Werkle-Bergner M, Kennedy BL, Guzman S, Hurth K, Miller CA, Qiao Y, Shi Y, Chui HC, Ringman JM. Locus coeruleus integrity is related to tau burden and memory loss in autosomal-dominant Alzheimer's disease. *Neurobiol Aging*. 2022 Apr;112:39-54. doi: 10.1016/j.neurobiolaging.2021.11.006. Epub 2021 Dec 7. PMID: 35045380; PMCID: PMC8976827.
20. Dahl, M. J., Mather, M., & Werkle-Bergner, M. (2022). Noradrenergic modulation of rhythmic neural activity shapes selective attention. *Trends in Cognitive Sciences*, 26(1), 38–52.
21. Dahl, M.J., Mather, M., Düzel, S. *et al*. Rostral locus coeruleus integrity is associated with better memory performance in older adults. *Nat Hum Behav* 3, 1203–1214 (2019). <https://doi.org/10.1038/s41562-019-0715-2>
22. Devilbiss DM, Waterhouse BD. Phasic and tonic patterns of locus coeruleus output differentially modulate sensory network function in the awake rat. *J Neurophysiol*. 2011 Jan;105(1):69-87. doi: 10.1152/jn.00445.2010. Epub 2010 Oct 27. PMID: 20980542; PMCID: PMC3023368.
23. Deyoung CG, Cicchetti D, Rogosch FA, Gray JR, Eastman M, Grigorenko EL. Sources of Cognitive Exploration: Genetic Variation in the Prefrontal Dopamine System Predicts Openness/Intellect. *J Res Pers*. 2011 Aug 1;45(4):364-371. doi: 10.1016/j.jrp.2011.04.002. PMID: 21804655; PMCID: PMC3143482.
24. DeYoung CG, Peterson JB, Higgins DM. Sources of openness/intellect: cognitive and neuropsychological correlates of the fifth factor of personality. *J Pers*. 2005 Aug;73(4):825-58. doi: 10.1111/j.1467-6494.2005.00330.x. PMID: 15958136.
25. Deyoung CG, Peterson JB, Séguin JR, Tremblay RE. Externalizing behavior and the higher order factors of the Big Five. *J Abnorm Psychol*. 2008 Nov;117(4):947-53. doi: 10.1037/a0013742. PMID: 19025240.
26. DeYoung CG, Quilty LC, Peterson JB, Gray JR. Openness to experience, intellect, and cognitive ability. *J Pers Assess*. 2014;96(1):46-52. doi: 10.1080/00223891.2013.806327. Epub 2013 Jun 24. PMID: 23795918.
27. Deyoung CG. The neuromodulator of exploration: A unifying theory of the role of dopamine in personality. *Front Hum Neurosci*. 2013 Nov 14;7:762. doi: 10.3389/fnhum.2013.00762. PMID: 24294198; PMCID: PMC3827581.
28. DeYoung, C. G. (2020). Intelligence and personality. In R. J. Sternberg (Ed.), *The Cambridge handbook of intelligence* (pp. 1011–1047). Cambridge University Press. <https://doi.org/10.1017/9781108770422.043>
29. Dutt, S., Li, Y., Mather, M. *et al*. Brainstem substructures and cognition in prodromal Alzheimer's disease. *Brain Imaging and Behavior* 15, 2572–2582 (2021). <https://doi.org/10.1007/s11682-021-00459-y>
30. Elman JA, Puckett OK, Beck A, Fennema-Notestine C, Cross LK, Dale AM, Eglit GML, Eyler LT, Gillespie NA, Granholm EL, Gustavson DE, Hagler DJ Jr, Hatton SN, Hauger R, Jak AJ, Logue MW, McEvoy LK, McKenzie RE,

- Neale MC, Panizzon MS, Reynolds CA, Sanderson-Cimino M, Toomey R, Tu XM, Whitsel N, Williams ME, Xian H, Lyons MJ, Franz CE, Kremen WS. MRI-assessed locus coeruleus integrity is heritable and associated with multiple cognitive domains, mild cognitive impairment, and daytime dysfunction. *Alzheimers Dement*. 2021 Jun;17(6):1017-1025. doi: 10.1002/alz.12261. Epub 2021 Feb 13. PMID: 33580733; PMCID: PMC8248066.
31. F. Naka, T. Shiga, M. Yaguchi, N. Okado An enriched environment increases noradrenaline concentration in the mouse brain *Brain Res*, 924 (2002), pp. 124-126
 32. factor model in discriminating specific mood and anxiety disorders. *Psychiatry Res*. 2012 Sep 30;199(2):131-9. doi: 10.1016/j.psychres.2012.04.027. Epub 2012 May 15. PMID: 22595418.
 33. Farley I.J., Hornykiewicz O. Noradrenaline distribution in subcortical areas of the human brain. *Brain Res*. 1977;126:53–62. doi: 10.1016/0006-8993(77)90214-1
 34. Fischer, R., Lee, A. & Verzijden, M.N. Dopamine genes are linked to Extraversion and Neuroticism personality traits, but only in demanding climates. *Sci Rep* 8, 1733 (2018). <https://doi.org/10.1038/s41598-017-18784-y>
 35. Fleeson W, Gallagher P. The implications of Big Five standing for the distribution of trait manifestation in behavior: fifteen experience-sampling studies and a meta-analysis. *J Pers Soc Psychol*. 2009 Dec;97(6):1097-114. doi: 10.1037/a0016786. PMID: 19968421; PMCID: PMC2791901.
 36. Forgeard M, Herzhoff K, Jayawickreme E, Tsukayama E, Beard C, Björgvinsson T. Changes in daily manifestations of Openness to Experience during intensive cognitive-behavioral treatment. *J Pers*. 2019 Aug;87(4):856-870. doi: 10.1111/jopy.12438. Epub 2018 Oct 28. PMID: 30317642.
 37. Franchow EI, Suchy Y, Thorgusen SR, Williams P (2013) More than Education: Openness to Experience Contributes to Cognitive Reserve in Older Adulthood. *Aging Sci* 1: 109. doi: 10.4172/2329-8847.1000109 C
 38. García-Gomar MG, Videnovic A, Singh K, Stauder M, Lewis LD, Wald LL, Rosen BR, Bianciardi M. Disruption of Brainstem Structural Connectivity in REM Sleep Behavior Disorder Using 7 Tesla Magnetic Resonance Imaging. *Mov Disord*. 2022 Apr;37(4):847-853. doi: 10.1002/mds.28895. Epub 2021 Dec 29. PMID: 34964520; PMCID: PMC9018552.
 39. George S., Mufson E., Leurgans S., Shah R., Ferrari C., Detolledo-Morrell L. MRI-based volumetric measurement of the substantia innominata in amnesic MCI and mild AD. *Neurobiol. Aging*. 2011;32:1756–1764. doi: 10.1016/j.neurobiolaging.2009.11.006
 40. Gnambs, Timo. (2014). A meta-analysis of dependability coefficients (test-retest reliabilities) for measures of the Big Five. *Journal of Research in Personality*. 52. 20-28. 10.1016/j.jrp.2014.06.003.
 41. Grella SL, Neil JM, Edison HT, Strong VD, Odintsova IV, Walling SG, Martin GM, Marrone DF, Harley CW. Locus Coeruleus Phasic, But Not Tonic, Activation Initiates Global Remapping in a Familiar Environment. *J Neurosci*. 2019 Jan 16;39(3):445-455. doi: 10.1523/JNEUROSCI.1956-18.2018. Epub 2018 Nov 26. PMID: 30478033; PMCID: PMC6335751.
 42. Grueschow M, Kleim B, Ruff CC. Functional Coupling of the Locus Coeruleus Is Linked to Successful Cognitive Control. *Brain Sci*. 2022 Feb 24;12(3):305. doi: 10.3390/brainsci12030305. PMID: 35326262; PMCID: PMC8946131.
 43. Herz N, Baror S, Bar M. Overarching States of Mind. *Trends Cogn Sci*. 2020 Mar;24(3):184-199. doi: 10.1016/j.tics.2019.12.015. Epub 2020 Feb 6. PMID: 32059121.
 44. Ihle A, Zuber S, Gouveia ÉR, Gouveia BR, Mella N, Desrichard O, Cullati S, Oris M, Maurer J, Kliegel M. Cognitive Reserve Mediates the Relation between Openness to Experience and Smaller Decline in Executive Functioning.

- Dement Geriatr Cogn Disord. 2019;48(1-2):39-44. doi: 10.1159/000501822. Epub 2019 Sep 11. PMID: 31509829.
45. Jackson JJ, Hill PL, Payne BR, Roberts BW, Stine-Morrow EA. Can an old dog learn (and want to experience) new tricks? Cognitive training increases openness to experience in older adults. *Psychol Aging*. 2012 Jun;27(2):286-92. doi: 10.1037/a0025918. Epub 2012 Jan 16. PMID: 22251379; PMCID: PMC3330146.
 46. Jacobs HIL, Becker JA, Kwong K, Engels-Domínguez N, Prokopiou PC, Papp KV, Properzi M, Hampton OL, d'Oleire Uquillas F, Sanchez JS, Rentz DM, El Fakhri G, Normandin MD, Price JC, Bennett DA, Sperling RA, Johnson KA. In vivo and neuropathology data support locus coeruleus integrity as indicator of Alzheimer's disease pathology and cognitive decline. *Sci Transl Med*. 2021 Sep 22;13(612):eabj2511. doi: 10.1126/scitranslmed.abj2511. Epub 2021 Sep 22. PMID: 34550726; PMCID: PMC8641759.
 47. Käckemester W, Bott A, Wacker J. Openness to experience predicts dopamine effects on divergent thinking. *Personal Neurosci*. 2019 Jul 26;2:e3. doi: 10.1017/pen.2019.3. PMID: 32435738; PMCID: PMC7219677.
 48. Kalbitzer J, Frokjaer VG, Erritzoe D, Svarer C, Cumming P, Nielsen FA, Hashemi SH, Baaré WF, Madsen J, Hasselbalch SG, Kringelbach ML, Mortensen EL, Knudsen GM. The personality trait openness is related to cerebral 5-HTT levels. *Neuroimage*. 2009 Apr 1;45(2):280-5. doi: 10.1016/j.neuroimage.2008.12.001. Epub 2008 Dec 14. PMID: 19135154.
 49. Kanen, J.W., Arntz, F.E., Yellowlees, R. et al. Serotonin depletion amplifies distinct human social emotions as a function of individual differences in personality. *Transl Psychiatry* 11, 81 (2021). <https://doi.org/10.1038/s41398-020-00880-9>
 50. Karsazi, Hossein & Rezapour, Tara & Kormi-Nouri, Reza & Mottaghi, Atieh & Abdekhodaie, Ehsan & Hatami, Javad. (2021). The Moderating Effect of Neuroticism and Openness in the Relationship between Age and Memory: Implications for Cognitive Reserve. *Personality and Individual Differences*. 10.1016/j.paid.2021.110773.
 51. Kaup AR, Harmell AL, Yaffe K. Conscientiousness Is Associated with Lower Risk of Dementia among Black and White Older Adults. *Neuroepidemiology*. 2019;52(1-2):86-92. doi: 10.1159/000492821. Epub 2019 Jan 2. PMID: 30602170.
 52. Keren N.I., Lozar C.T., Harris K., Morgan P, Eckert M.A. In vivo mapping of the human locus coeruleus. *NeuroImage*. 2009;47:1261–1267. doi: 10.1016/j.neuroimage.2009.06.012
 53. Keren N.I., Taheri S., Vazey E.M., Morgan P, Granholm A.-C.E., Aston-Jones G.S., Eckert M.A. Histologic validation of locus coeruleus MRI contrast in post-mortem tissue. *NeuroImage*. 2015;113:235–245. doi: 10.1016/j.neuroimage.2015.03.020
 54. Kilimann I., Grothe M., Heinsen H., Alho E.J.L., Grinberg L., Jr E.A., Dos Santos G.A.B., Da Silva R.E., Mitchell A.J., Frisoni G.B., et al. Subregional Basal Forebrain Atrophy in Alzheimer's Disease: A Multicenter Study. *J. Alzheimer's Dis*. 2014;40:687–700. doi: 10.3233/JAD-132345
 55. Kirby L., Pernar L., Valentino R., Beck S. Distinguishing characteristics of serotonin and non-serotonin-containing cells in the dorsal raphe nucleus: Electrophysiological and immunohistochemical studies. *Neuroscience*. 2003;116:669–683. doi: 10.1016/S0306-4522(02)00584-5.
 56. Koulousakis P, Andrade P, Visser-Vandewalle V, Sesia T. The Nucleus Basalis of Meynert and Its Role in Deep Brain Stimulation for Cognitive Disorders: A Historical Perspective. *J. Alzheimer's Dis*. 2019;69:905–919. doi: 10.3233/jad-180133
 57. Krebs RM, Fias W, Achten E, Boehler CN. Picture novelty attenuates semantic interference and modulates concomitant neural activity in the anterior cingulate cortex and the locus coeruleus. *Neuroimage*. 2013 Jul

- 1;74:179-87. doi: 10.1016/j.neuroimage.2013.02.027. Epub 2013 Feb 21. PMID: 23454569.
58. Krebs RM, Park HRP, Bombeke K, Boehler CN. Modulation of locus coeruleus activity by novel oddball stimuli. *Brain Imaging Behav.* 2018 Apr;12(2):577-584. doi: 10.1007/s11682-017-9700-4. PMID: 28271441.
59. Liu A.K.L., Chang R.C.-C., Pearce R.K.B., Gentleman S.M. Nucleus basalis of Meynert revisited: Anatomy, history and differential involvement in Alzheimer's and Parkinson's disease. *Acta Neuropathol.* 2015;129:527–540. doi: 10.1007/s00401-015-1392-5
60. Liu K.Y., Acosta-Cabronero J., Cardenas-Blanco A., Loane C., Berry A., Betts M., Kievit R.A., Henson R., Düzel E., Howard R., et al. In vivo visualization of age-related differences in the locus coeruleus. *Neurobiol. Aging.* 2019;74:101–111. doi: 10.1016/j.neurobiolaging.2018.10.014.
61. Liu, K.Y., Kievit, R.A., Tsvetanov, K.A. et al. Noradrenergic-dependent functions are associated with age-related locus coeruleus signal intensity differences. *Nat Commun* 11, 1712 (2020). <https://doi.org/10.1038/s41467-020-15410-w>
62. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* 2020 Aug 8;396(10248):413-446. doi: 10.1016/S0140-6736(20)30367-6. Epub 2020 Jul 30. PMID: 32738937; PMCID: PMC7392084.
63. Luchetti M, Terracciano A, Stephan Y, Sutin AR. Personality and cognitive decline in older adults: data from a longitudinal sample and meta-analysis. *J Gerontol B Psychol Sci Soc Sci.* 2016;71:591–601.
64. M. Grilli, S. Zappettini, A. Zanardi, F. Lagomarsino, A. Pittaluga, M. Zoli, M. Marchi. **Exposure to an enriched environment selectively increases the functional response of the pre-synaptic NMDA receptors which modulate noradrenaline release in mouse hippocampus** *J. Neurochem*, 110 (2009), pp. 1598-1606
65. Mai J.K., Paxinos G. *The Human Nervous System*. 3rd ed. Academic Press; Cambridge, MA, USA: 2012
66. Martin LR, Friedman HS, Schwartz JE. Personality and mortality risk across the life span: the importance of conscientiousness as a biopsychosocial attribute. *Health Psychol.* 2007 Jul;26(4):428-36. doi: 10.1037/0278-6133.26.4.428. PMID: 17605562.
67. Matchett, B.J., Grinberg, L.T., Theofilas, P. et al. The mechanistic link between selective vulnerability of the locus coeruleus and neurodegeneration in Alzheimer's disease. *Acta Neuropathol* 141, 631–650 (2021). <https://doi.org/10.1007/s00401-020-022481>
68. Mather M, Harley CW. The Locus Coeruleus: Essential for Maintaining Cognitive Function and the Aging Brain. *Trends Cogn Sci.* 2016 Mar;20(3):214-226. doi: 10.1016/j.tics.2016.01.001. PMID: 26895736; PMCID: PMC4761411.
69. Mather M. Noradrenaline in the aging brain: Promoting cognitive reserve or accelerating Alzheimer's disease? *Semin Cell Dev Biol.* 2021 Aug;116:108-124. doi: 10.1016/j.semcdb.2021.05.013. Epub 2021 Jun 4. PMID: 34099360; PMCID: PMC8292227.
70. McCrae RR, Kurtz JE, Yamagata S, Terracciano A. Internal consistency, retest reliability, and their implications for personality scale validity. *Pers Soc Psychol Rev.* 2011 Feb;15(1):28-50. doi: 10.1177/1088868310366253. Epub 2010 Apr 30. PMID: 20435807; PMCID: PMC2927808.
71. Moutafi J., Furnham A., Crump J., What facets of openness and conscientiousness predict fluid intelligence score?, *Learning and Individual Differences*. Volume 16, Issue 1, 2006, Pages 31-42, ISSN 1041-6080,

- Anglim, J., Dunlop, P. D., Wee, S., Horwood, S., Wood, J. K., & Marty, A. (2022). Personality and intelligence: A meta-analysis. *Psychological Bulletin*, 148(5-6), 301–336. <https://doi.org/10.1037/bul0000373>
72. Narita S, Iwahashi K, Nagahori K, Numajiri M, Yoshihara E, Ohtani N, Ishigooka J. Analysis of Association between Norepinephrine Transporter Gene Polymorphisms and Personality Traits of NEO-FFI in a Japanese Population. *Psychiatry Investig*. 2015 Jul;12(3):381-7. doi: 10.4306/pi.2015.12.3.381. Epub 2015 Jul 6. PMID: 26207133; PMCID: PMC4504922.
73. Omoluabi T, Torraville SE, Maziar A, Ghosh A, Power KD, Reinhardt C, Harley CW, Yuan Q. Novelty-like activation of locus coeruleus protects against deleterious human pretangle tau effects while stress-inducing activation worsens its effects. *Alzheimers Dement (N Y)*. 2021 Dec 31;7(1):e12231. doi: 10.1002/trc2.12231. PMID: 35005208; PMCID: PMC8719346.
74. Ordway G.A., Stockmeier C.A., Cason G.W., Klimek V. Pharmacology and Distribution of Norepinephrine Transporters in the Human Locus Coeruleus and Raphe Nuclei. *J. Neurosci*. 1997;17:1710–1719. doi: 10.1523/JNEUROSCI.17-05-01710.1997.
75. Pauli W.M., Nili A.N., Tyszka J.M. A high-resolution probabilistic in vivo atlas of human subcortical brain nuclei. *Sci. Data*. 2018;5:180063. doi: 10.1038/sdata.2018.63
76. Plini ERG, O'Hanlon E, Boyle R, Sibilia F, Rikhye G, Kenney J, Whelan R, Melnychuk MC, Robertson IH, Dockree PM. Examining the Role of the Noradrenergic Locus Coeruleus for Predicting Attention and Brain Maintenance in Healthy Old Age and Disease: An MRI Structural Study for the Alzheimer's Disease Neuroimaging Initiative. *Cells*. 2021 Jul 20;10(7):1829. doi: 10.3390/cells10071829. PMID: 34359997; PMCID: PMC8306442.
77. Prokopiou PC, Engels-Domínguez N, Papp KV, Scott MR, Schultz AP, Schneider C, Farrell ME, Buckley RF, Quiroz YT, El Fakhri G, Rentz DM, Sperling RA, Johnson KA, Jacobs HIL. Lower novelty-related locus coeruleus function is associated with A β -related cognitive decline in clinically healthy individuals. *Nat Commun*. 2022 Mar 23;13(1):1571. doi: 10.1038/s41467-022-28986-2. PMID: 35322012; PMCID: PMC8943159.
78. Rammstedt B, Lechner CM, Danner D. Relationships between Personality and Cognitive Ability: A Facet-Level Analysis. *J Intell*. 2018 May 18;6(2):28. doi: 10.3390/jintelligence6020028. PMID: 31162455; PMCID: PMC6480763.
79. Ren Z, Liu C, Meng J, Liu Q, Shi L, Wu X, Song L, Qiu J. Effects of the Openness to Experience Polygenic Score on Cortical Thickness and Functional Connectivity. *Front Neurosci*. 2021 Jan 11;14:607912. doi: 10.3389/fnins.2020.607912. PMID: 33505240; PMCID: PMC7829912.
80. Rhodes, R. E., & Smith, N. E. (2006). Personality correlates of physical activity: a review and meta-analysis. *British journal of sports medicine*, 40(12), 958–965. <https://doi.org/10.1136/bjsm.2006.028860>
81. Robertson I.H. A noradrenergic theory of cognitive reserve: Implications for Alzheimer's disease. *Neurobiol. Aging*. 2013;34:298–308. doi: 10.1016/j.neurobiolaging.2012.05.019
82. Robertson I.H. A right hemisphere role in cognitive reserve. *Neurobiol. Aging*. 2014;35:1375–1385. doi: 10.1016/j.neurobiolaging.2013.11.028
83. Rong Y., Rua C., O'Callaghan C., Jones P.S., Hezemans F., Kaalund S.S., Tsvetanov K.A., Rodgers C.T., Williams G., Passamonti L., et al. An in vivo Probabilistic Atlas of the Human Locus Coeruleus at Ultra-high Field. *bioRxiv*. 2020 doi: 10.1101/2020.02.03.932087
84. Schmidt, K. H. & Metzler, P. *WST: Wortschatztest*. (Beltz, 1992)

85. Schretlen DJ, van der Hulst EJ, Pearlson GD, Gordon B. A neuropsychological study of personality: trait openness in relation to intelligence, fluency, and executive functioning. *J Clin Exp Neuropsychol*. 2010 Dec;32(10):1068-73. doi: 10.1080/13803391003689770. Epub 2010 Apr 19. PMID: 20408002; PMCID: PMC2937090.
86. Schulz J., Pagano G., Bonfante J.A.F., Wilson H., Politis M. Nucleus basalis of Meynert degeneration precedes and predicts cognitive impairment in Parkinson's disease. *Brain*. 2018;141:1501–1516. doi: 10.1093/brain/awy072
87. Sharp ES, Reynolds CA, Pedersen NL, Gatz M. Cognitive engagement and cognitive aging: is openness protective? *Psychol Aging*. 2010 Mar;25(1):60-73. doi: 10.1037/a0018748. PMID: 20230128; PMCID: PMC2853722.
88. Stern Y. Cognitive reserve. *Neuropsychologia*. 2009;47:2015–2028. doi: 10.1016/j.neuropsychologia.2009.03.004.
89. Stern Y, Urquijo E.M.A., Bartrés-Faz D., Belleville S., Cantillon M., Chetelat G., Ewers M., Franzmeier N., Kempermann G., Kremen W.S., et al. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's Dement*. 2020;16:1305–1311. doi: 10.1016/j.jalz.2018.07.219
90. Sutin AR (B), Stephan Y, Damian RI, Luchetti M, Strickhouser JE, Terracciano A. Five-factor model personality traits and verbal fluency in 10 cohorts. *Psychol Aging*. 2019;34(3):362–73.
91. Sutin AR, Ferrucci L, Zonderman AB, Terracciano A. Personality and obesity across the adult life span. *J Pers Soc Psychol*. 2011 Sep;101(3):579-92. doi: 10.1037/a0024286. PMID: 21744974; PMCID: PMC3462003.
92. Sutin AR, Stephan Y, Luchetti M, Artese A, Oshio A, Terracciano A. The five factor model of personality and physical inactivity: a meta-analysis of 16 samples. *J Res Pers*. 2016;63:22–8.
93. Sutin AR, Stephan Y, Terracciano A. Facets of Conscientiousness and risk of dementia. *Psychol Med*. 2018 Apr;48(6):974-982. doi: 10.1017/S0033291717002306. Epub 2017 Sep 6. PMID: 28874220; PMCID: PMC5839940.
94. Sutin, A.R., Stephan, Y., Luchetti, M. et al. Five-factor model personality traits and cognitive function in five domains in older adulthood. *BMC Geriatr* 19, 343 (2019). <https://doi.org/10.1186/s12877-019-1362-1>
95. Tautvydaitė D, Kukreja D, Antonietti JP, Henry H, von Gunten A, Popp J. Interaction between personality traits and cerebrospinal fluid biomarkers of Alzheimer's disease pathology modulates cognitive performance. *Alzheimers Res Ther*. 2017 Feb 2;9(1):6. doi: 10.1186/s13195-017-0235-0. PMID: 28153054; PMCID: PMC5290611.
96. Terracciano A, Stephan Y, Luchetti M, Albanese E, Sutin AR. Personality traits and risk of cognitive impairment and dementia. *J Psychiatr Res*. 2017 Jun;89:22-27. doi: 10.1016/j.jpsychires.2017.01.011. Epub 2017 Jan 22. PMID: 28153642; PMCID: PMC5374012.
97. Tochigi M, Otowa T, Hibino H, Kato C, Otani T, Umekage T, Utsumi T, Kato N, Sasaki T. Combined analysis of association between personality traits and three functional polymorphisms in the tyrosine hydroxylase, monoamine oxidase A, and catechol-O-methyltransferase genes. *Neurosci Res*. 2006 Mar;54(3):180-5. doi: 10.1016/j.neures.2005.11.003. Epub 2005 Dec 19. PMID: 16360899.
98. Tona K.-D., Keuken M., De Rover M., Lakke E., Forstmann B.U., Nieuwenhuis S., Van Osch M.J.P. In vivo visualization of the locus coeruleus in humans: Quantifying the test–retest reliability. *Brain Struct. Funct*. 2017;222:4203–4217. doi: 10.1007/s00429-017-1464-5

99. Tsukahara JS, Engle RW. Fluid intelligence and the locus coeruleus-norepinephrine system. *Proc Natl Acad Sci U S A*. 2021 Nov 16;118(46):e2110630118. doi: 10.1073/pnas.2110630118. PMID: 34764223; PMCID: PMC8609644.
100. Unsworth, N., Robison, M.K. A locus coeruleus-norepinephrine account of individual differences in working memory capacity and attention control. *Psychon Bull Rev* **24**, 1282–1311 (2017).
<https://doi.org/10.3758/s13423-016-1220-5>
101. Veyrac A., J. Sacquet, V. Nguyen, M. Marien, F. Jourdan, A. Didier **Novelty determines the effects of olfactory enrichment on memory and neurogenesis through noradrenergic mechanisms.** *Neuropsychopharmacology*, 34 (2009), pp. 786-795
102. Ward R, Sreenivas S, Read J, Saunders KEA, Rogers RD. The role of serotonin in personality inference: tryptophan depletion impairs the identification of neuroticism in the face. *Psychopharmacology (Berl)*. 2017 Jul;234(14):2139-2147. doi: 10.1007/s00213-017-4619-4. Epub 2017 May 9. PMID: 28488040; PMCID: PMC5486943.
103. Wilson R.S., Nag S., Boyle P.A., Hize L., Yu L., Buchman A.S., Schneider J.A., Bennett D.A. Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. *Neurology*. 2013;80:1202–1208.
doi: 10.1212/WNL.0b013e3182897103
104. Wilson RS, Schneider JA, Arnold SE, Bienias JL, Bennett DA. Conscientiousness and the incidence of Alzheimer disease and mild cognitive impairment. *Arch Gen Psychiatry*. 2007 Oct;64(10):1204-12. doi: 10.1001/archpsyc.64.10.1204. PMID: 17909133.
105. Yoneda T, Graham E, Lozinski T, Bennett DA, Mroczek D, Piccinin AM, Hofer SM, Muniz-Terrera G. Personality traits, cognitive states, and mortality in older adulthood. *J Pers Soc Psychol*. 2022 Apr 11;10.1037/pspp0000418. doi: 10.1037/pspp0000418. Epub ahead of print. PMID: 35404649; PMCID: PMC9550879.
106. Zaborszky L., Hoemke L., Mohlberg H., Schleicher A., Amunts K., Zilles K. Stereotaxic probabilistic maps of the magnocellular cell groups in human basal forebrain. *Neuroimage*. 2008;42:1127–1141.
doi: 10.1016/j.neuroimage.2008.05.055
107. Zhao, M., Kong, L. & Qu, H. A systems biology approach to identify intelligence quotient score-related genomic regions and pathways relevant to potential therapeutic treatments. *Sci Rep* 4, 4176 (2014).
<https://doi.org/10.1038/srep04176>
108. Zmorzyński, S., Styk, W., Klinkosz, W. et al. Personality traits and polymorphisms of genes coding neurotransmitter receptors or transporters: review of single gene and genome-wide association studies. *Ann Gen Psychiatry* 20, 7 (2021). <https://doi.org/10.1186/s12991-021-00328-4>
109. Rorabaugh JM, Chalampalanupap T, Botz-Zapp CA, Fu VM, Lembeck NA, Cohen RM, Weinshenker D. Chemogenetic locus coeruleus activation restores reversal learning in a rat model of Alzheimer's disease. *Brain*. 2017 Nov 1;140(11):3023-3038. doi: 10.1093/brain/awx232. PMID: 29053824; PMCID: PMC5841201.
110. Ghosh A, Massaeli F, Power KD, Omoluabi T, Torraville SE, Pritchett JB, Sepahvand T, Strong VD, Reinhardt C, Chen X, Martin GM, Harley CW, Yuan Q. Locus Coeruleus Activation Patterns Differentially Modulate Odor Discrimination Learning and Odor Valence in Rats. *Cereb Cortex Commun*. 2021 Apr 5;2(2):tgab026. doi: 10.1093/texcom/tgab026. PMID: 34296171; PMCID: PMC8152946.
111. Sara, S. J., Vankov, A., & Hervé, A. (1994). Locus coeruleus-evoked responses in behaving rats: A clue to the role of noradrenaline in memory. *Brain Research Bulletin*, 35(5-6), 457–465. doi:10.1016/0361-9230(94)90159-7

Tables

Tables 1-4 are available in the supplementary files section.

Figures

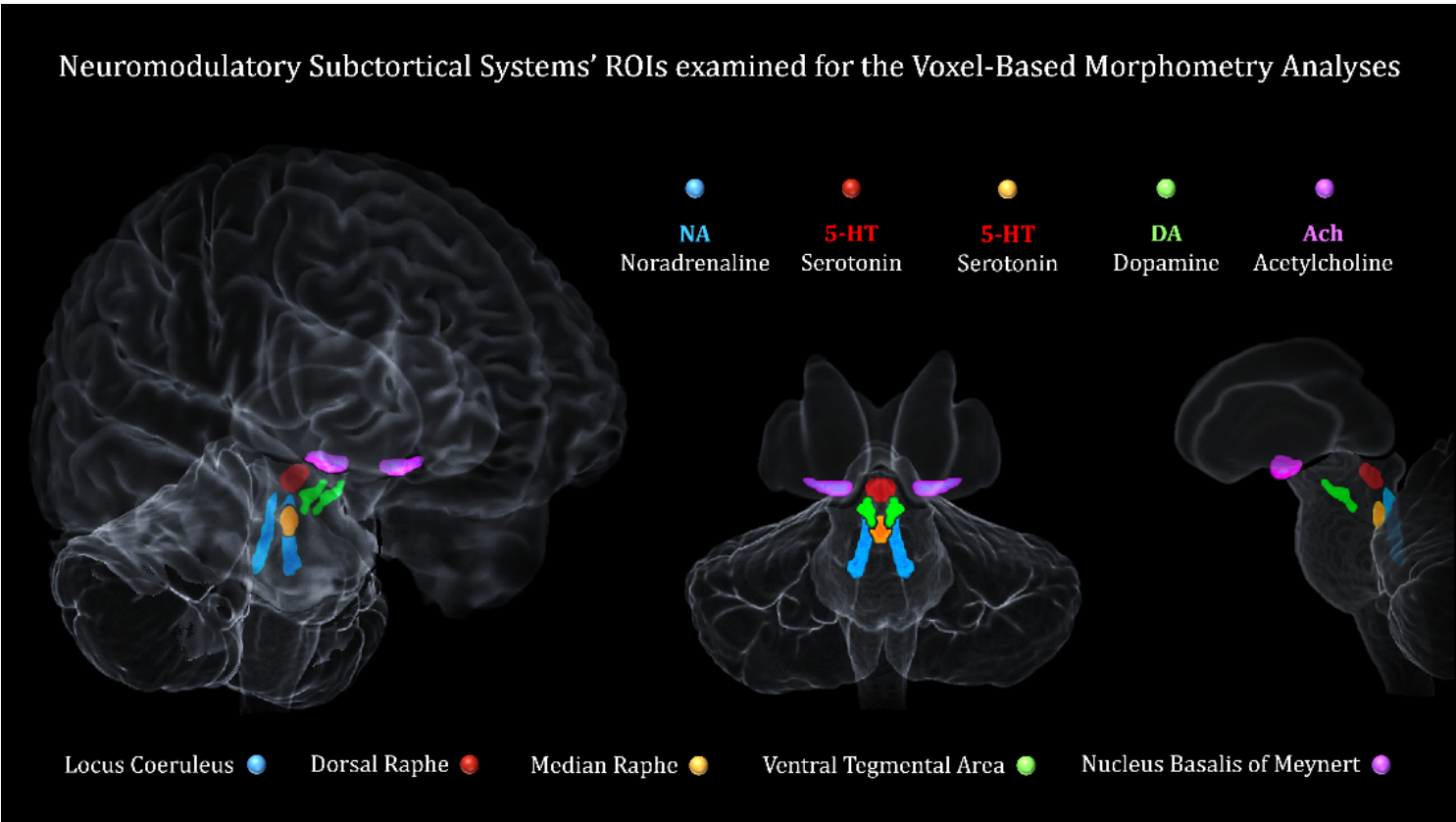


Figure 1

Neuromodulatory subcortical system. The five ROIs considered for the voxel-based morphometry analyses. In blue is shown the Locus Coeruleus (LC - noradrenaline), in orange the Median Raphe (MR - Serotonin), in red the Dorsal Raphe (DR - Serotonin), in green the Ventral Tegmental Area (VTA - Dopamine), in purple the Nucleus Basalis of Meynert (NBM - Acetylcholine)

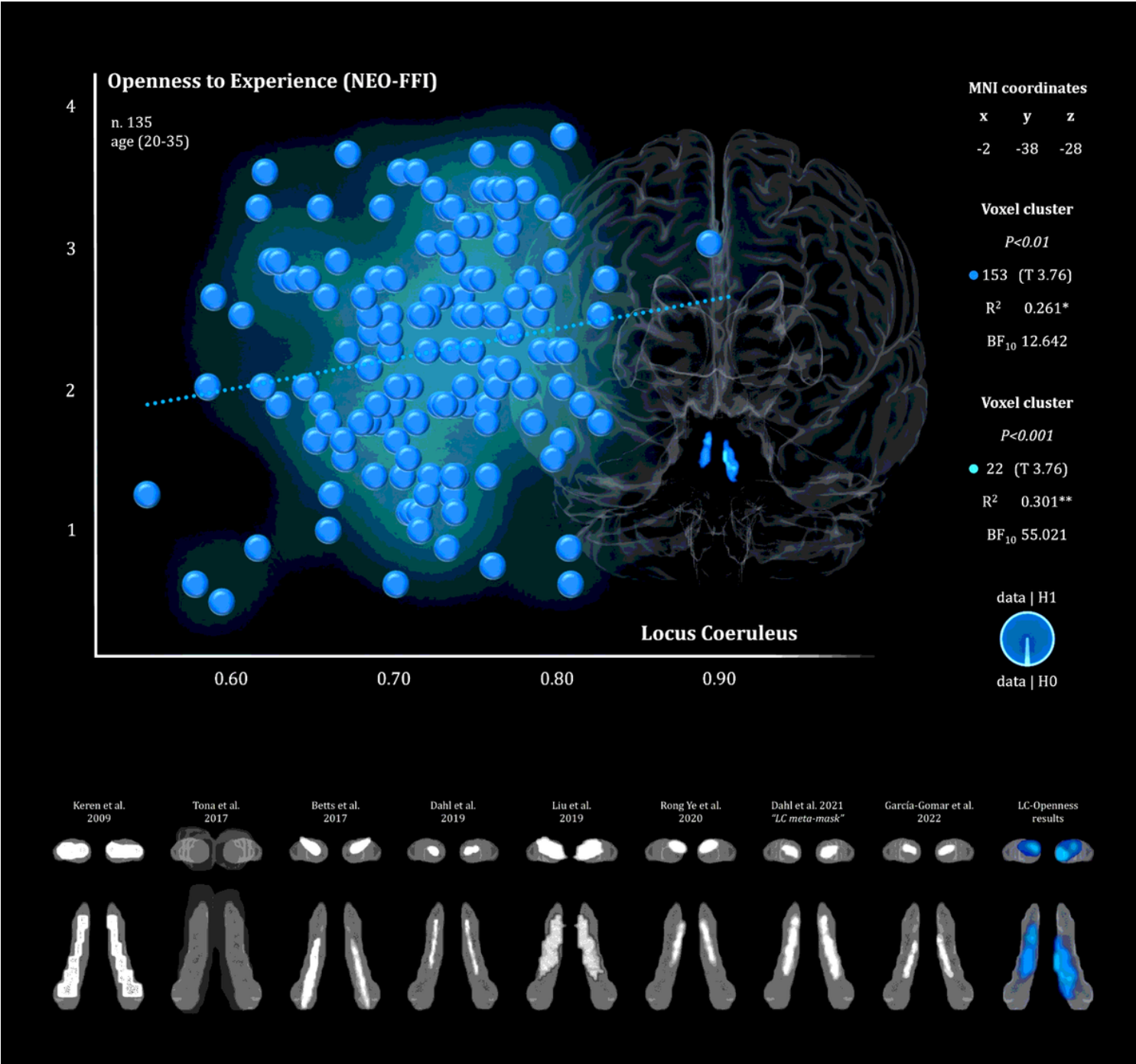


Figure 2

The upper portion of the figure shows the relationship between Openness to Experience (NEO-FFI) and Locus Coeruleus MRI signal intensity across n.135 healthy young subjects (age range 20-35) for $P < 0.001$ threshold. The results are corrected for age, gender and total intracranial volume. The significant LC cluster (in blue) is shown on a coronal 3D reconstruction of the brain. MNI coordinates and statistical threshold along with Bayes Factors are reported on the right portion of the figure. Greater LC signal intensity is related with greater OE scores. Below the LC findings are shown in comparison with the spatial resolution of the previously published LC MRI masks and atlases. The images are displayed on a 3D LC reconstruction by Plini et al. 2021. shown from axial and coronal point of views.

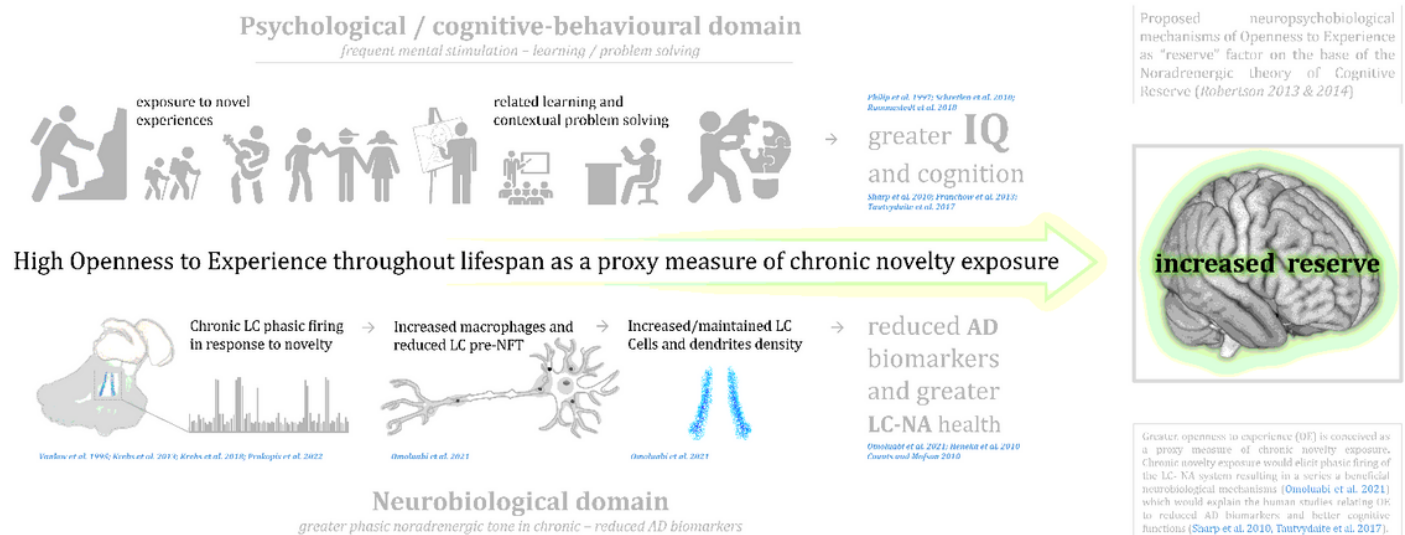


Figure 3

Graphical discussion: Proposed neuropsychobiological mechanisms of Openness to Experience as “reserve” factor on the base of the Noradrenergic theory of Cognitive Reserve (Robertson 2013 & 2014). Greater openness to experience (OE) is conceived as a proxy measure of chronic novelty exposure. Chronic novelty exposure would elicit phasic firing of the LC-NA system resulting in a series of beneficial neurobiological mechanisms (Rorabaugh et al. 2017; Ghosh et al. 2021; Omoluabi et al. 2021) which would explain the human studies relating OE to reduced AD biomarkers and better cognitive functions (Sharp et al. 2010, Tautvydaite et al. 2017).

While the nature of the observed relationship between LC and OE is correlational, it should be considered that the other experiments reported causal effects of “novelty-like” LC activations and reduced biomarkers of neurodegeneration. However, it should be taken into account that the proposed underlining mechanisms might be explained by other variables and potentially reside also within other neurobiological/neuropsychological pathways.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Tables.docx](#)
- [SupplementaryMaterials310723.docx](#)